CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 18117/S029

APPROVAL LETTER

DIV

FEB - 8 1999

NDA 18-117/S-029

Rhone-Poulenc Rorer Pharmaceuticals, Inc.
500 Arcola Road
Collegeville, PA 19426-0107

Attention: Judith R. Plon
Director, Regulatory Affairs

Dear Ms. Plon:

Please refer to your supplemental new drug application dated September 3, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azmacort (triamcinolone acetonide) Inhalation Aerosol.

This supplemental new drug application provides for addition of priming information to the package insert, Information for the Patient Sheet and carton labeling.

We have completed the review of this supplemental application, and it is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert, Information for the Patient Sheet, and carton label submitted September 3, 1998).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 18-117/S-029." Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Sandy Barnes, Project Manager, at (301) 827-1075.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 18117/S029

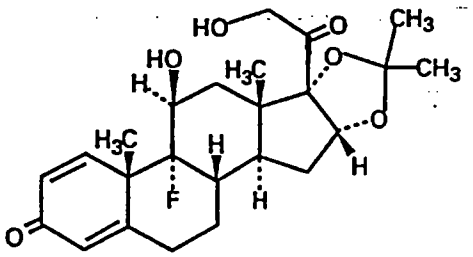
FINAL PRINTED LABELING

IN-0367J
Rev. 6/97

APPROVED
FEB - 8 1999

Azmacort®
(triamcinolone acetonide)
Inhalation Aerosol
For Oral Inhalation Only
Shake Well Before Using

DESCRIPTION
Triamcinolone acetonide, USP, the active ingredient in Azmacort® Inhalation Aerosol, is a corticosteroid with a molecular weight of 434.5 and with the chemical designation 9-Fluoro-11ß,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone. ($C_{24}H_{31}FO_6$).



Azmacort Inhalation Aerosol is a metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in the propellant dichlorodifluoromethane and dehydrated alcohol USP 1% w/w. Each canister contains 60 mg triamcinolone acetonide. The canister must be primed prior to the first use. After an initial priming of 2 actuations, each actuation delivers 200 mcg triamcinolone acetonide from the valve and 100 mcg from the spacer-mouthpiece under defined *in vitro* test conditions. The canister will remain primed for 3 days. If the canister is not used for more than 3 days, then it should be reprimed with 2 actuations. There are at least 240 actuations in one **Azmacort** Inhalation Aerosol canister. **After 240 actuations, the amount delivered per actuation may not be consistent and the unit should be discarded.**

CLINICAL PHARMACOLOGY
Triamcinolone acetonide is a more potent derivative of triamcinolone. Although triamcinolone itself is approximately one to two times as potent as prednisone in animal models of inflammation, triamcinolone acetonide is approximately 8 times more potent than prednisone.

The precise mechanism of the action of glucocorticoids in asthma is unknown. However, the inhaled route makes it possible to provide effective local anti-inflammatory activity with reduced systemic corticosteroid effects. Though highly effective for asthma, glucocorticoids do not affect asthma symptoms immediately. While improvement in asthma may occur as soon as one week after initiation of

Azmacort Inhalation Aerosol therapy, maximum improvement may not be achieved for 2 weeks or longer.

Based upon intravenous dosing of triamcinolone acetonide phosphate ester, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (Vd) reported was 99.5 L (SD ± 27.5) and clearance was 45.2 L/hour (SD ± 9.1) for triamcinolone acetonide. The plasma half-life of glucocorticoids does not correlate well with the biologic half-life.

The pharmacokinetics of radiolabeled triamcinolone acetonide [^{14}C] were evaluated following a single oral dose of 800 mcg to healthy male volunteers. Radiolabeled triamcinolone acetonide was found to undergo relatively rapid absorption following oral administration with maximum plasma triamcinolone acetonide and [^{14}C]-derived radioactivity occurring between 1.5 and 2 hours. Plasma protein binding of triamcinolone acetonide appears to be relatively low and consistent over a wide plasma triamcinolone acetonide concentration range as a function of time. The overall mean percent fraction bound was approximately 68%.

The metabolism and excretion of triamcinolone acetonide were both rapid and extensive with no parent compound being detected in the plasma after 24 hours post-dose and a low ratio (10.6%) of parent compound $AUC_{0-\infty}$ to total [^{14}C] radioactivity $AUC_{0-\infty}$. Greater than 90% of the oral [^{14}C]-radioactive dose was recovered within 5 days after administration in 5 out of the 6 subjects in the study. Of the recovered [^{14}C]-radioactivity, approximately 40% and 60% were found in the urine and feces, respectively.

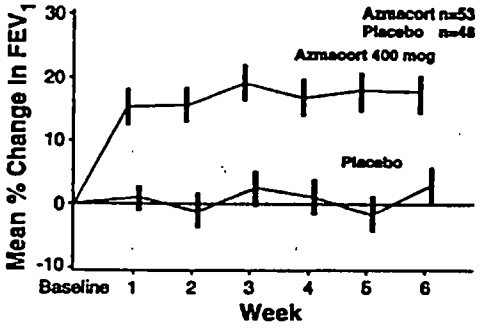
Three metabolites of triamcinolone acetonide have been identified. They are 6ß-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6ß-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

CLINICAL TRIALS

Double-blind, placebo controlled efficacy and safety studies have been conducted in asthma patients with a range of asthma severities, from those patients with mild disease to those with severe disease requiring oral steroid therapy.

The efficacy and safety of **Azmacort** Inhalation Aerosol given twice daily was demonstrated in two placebo-controlled clinical trials. In two separate studies, 222 asthmatic patients were randomized to receive either **Azmacort** Inhalation Aerosol 400 mcg twice daily or matching placebo for a treatment period of 6 weeks. Patients were adult asthmatics who were using inhaled beta$_2$-agonists on more than an occasional basis (at least three times weekly), either without or with inhaled corticosteroids, for control of their asthma symptoms. For the combined studies, 48% (52/109) patients randomized to placebo and 41% (46/113) patients randomized to **Azmacort** treatment were previously treated with inhaled corticosteroids.

Results of weekly lung function tests (FEV_1) from one of these trials is presented graphically below. Results of the second study are presented in tabular form as the changes in asthma measures from baseline to the end of the treatment period.



Mean Changes in Asthma Measures from Baseline to Endpoint[a]
All-Treated Patients
Results from a Placebo-Controlled, 6 Week Study

Asthma Measure	Placebo (N=61)	Azmacort 400 mcg bid (N=60)
Percent Change in FEV_1(%)	2.8%	17.5%
Increase in Morning Peak Flow Rate (L/min)	6.7	45.9
Decrease in Albuterol Use (puffs/day)	0.6	3.4
Decrease in Daily Asthma Symptom Score (units/day)[b]	0.5	2.3

[a]Endpoint Results are obtained from the last evaluable data, regardless of whether the patient completed 6 weeks of treatment

[b]Scale (0-6) with 0 = no symptom: Maximum Score (AM + PM) =12

In both studies, treatment with **Azmacort** Inhalation Aerosol (400 mcg twice daily) resulted in significant improvements in all clinical asthma measures (lung functions, asthma symptoms, use of as-needed $beta_2$-agonist medications) when compared to placebo.

INDICATIONS

Azmacort Inhalation Aerosol is indicated in the maintenance treatment of asthma as prophylactic therapy. **Azmacort** Inhalation Aerosol is also indicated for asthma patients who require systemic corticosteroid administration, where adding Azmacort may reduce or eliminate the need for the systemic corticosteroids.

Azmacort Inhalation Aerosol is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Azmacort Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to triamcinolone acetonide or any of the other ingredients in this preparation contraindicates its use.

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to **Azmacort** Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosolized steroids in recommended doses. After withdrawal from systemic corticosteroids, a number of months is usually required for recovery of hypothalamic-pituitary-adrenal (HPA) function. For some patients who have received large doses of oral steroids for long periods of time before therapy with **Azmacort** Inhalation Aerosol is initiated, recovery may be delayed for one year or longer. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infections, particularly gastroenteritis or other conditions with acute electrolyte loss. Although **Azmacort** Inhalation Aerosol may provide control of asthmatic symptoms during these episodes, in recommended doses it supplies only normal physiological amounts of corticosteroid systemically and does NOT provide the increased systemic steroid which is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been recently withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack.

Localized infections with *Candida albicans* have occurred infrequently in the mouth and pharynx. These areas should be examined by the treating physician at each patient visit. The percentage of positive mouth and throat cultures for *Candida albicans* did not change during a year of continuous therapy. The incidence of clinically apparent infection is low (2.5%). These infections may disappear spontaneously or may require treatment with appropriate antifungal therapy or discontinuance of treatment with **Azmacort** Inhalation Aerosol.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Azmacort Inhalation Aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing following dosing. If bronchospasm occurs following use of **Azmacort** Inhalation Aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with **Azmacort** Inhalation Aerosol should be discontinued and alternative treatment should be instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma which are not responsive to bronchodilators occur during the course of treatment with **Azmacort** Inhalation Aerosol. During such episodes, patients may require therapy with systemic corticosteroids.

The use of **Azmacort** Inhalation Aerosol with systemic prednisone, dosed either daily or on alternate-days, could increase the likelihood of HPA suppression compared to a therapeutic dose of either one alone. Therefore, **Azmacort** Inhalation Aerosol should be used with caution in patients already receiving prednisone treatment for any disease.

Transfer of patients from systemic steroid therapy to **Azmacort** Inhalation Aerosol may unmask allergic conditions previously suppressed by the systemic steroid therapy, *e.g.*, rhinitis, conjunctivitis, and eczema.

PRECAUTIONS

During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. (See **DOSAGE AND ADMINISTRATION.**) Although steroid withdrawal effects are usually transient and not severe, severe and even fatal exacerbation of asthma can occur if the previous daily oral corticosteroid requirement had significantly exceeded 10 mg/day of prednisone or equivalent.

In responsive patients, inhaled corticosteroids will often permit control of asthmatic symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since triamcinolone acetonide is absorbed into the circulation and can be systemically active, the beneficial effects of **Azmacort** Inhalation Aerosol in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

Suppression of HPA function has been reported in volunteers who received 4000 mcg daily of triamcinolone acetonide by oral inhalation. In addition, suppression of HPA function has been reported in some patients who have received recommended doses for as little as 6 to 12 weeks. Since the response of HPA function to inhaled corticosteroids is highly individualized, the physician should consider this information when treating patients.

When used at excessive doses or at recommended doses in a small number of susceptible individuals, systemic corticosteroid effects such as hypercorticoidism and adrenal suppression may appear. If such changes occur, **Azmacort** Inhalation Aerosol should be discontinued slowly, consistent with accepted procedures for reducing systemic steroid therapy and for management of asthma symptoms.

Azmacort Inhalation Aerosol should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, parasitic, or viral infections; or ocular herpes simplex.

The long-term local and systemic effects of **Azmacort** Inhalation Aerosol in human subjects are still not fully known. While there has been no clinical evidence of adverse experiences, the effects resulting from chronic use of **Azmacort** Inhalation Aerosol on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects including suppression of growth in children. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of a decrease in adrenal function.

Information for Patients: Patients being treated with **Azmacort** Inhalation Aerosol should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a complete disclosure of all possible adverse or intended effects.

Patients should use **Azmacort** Inhalation Aerosol at regular intervals as directed. Results of clinical trials indicate that significant improvement in asthma may occur by 1 week, but maximum benefit may not be achieved for 2 weeks or more. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

In clinical studies and post-marketing experience with **Azmacort** Inhalation Aerosol, local infections of the oropharynx with *Candida albicans* have occurred. When such an infection develops, it should be treated with appropriate local or systemic (*i.e.*, oral antifungal) therapy while remaining on treatment with **Azmacort** Inhalation Aerosol. However, at times therapy with **Azmacort** Inhalation Aerosol may need to be interrupted.

Patients should be instructed to track their use of **Azmacort** Inhalation Aerosol and to dispose of the canister after 240 actuations since reliable dose delivery cannot be assured after 240 doses.

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of treatment-related carcinogenicity was demonstrated after two years of once daily gavage of triamcinolone acetonide at doses of 0.05, 0.2, and 1.0 mcg/kg (approximately 0.02, 0.07, and 0.4% of the maximum recommended human daily inhalation dose on a mcg/m^2 basis) in the rat and 0.1, 0.6, and 3.0 mcg/kg (approximately 0.02, 0.1, and 0.6% of the maximum recommended human daily inhalation dose on a mcg/m^2 basis) in a mouse.

Mutagenesis studies with triamcinolone acetonide have not been carried out.

No evidence of impaired fertility was manifested when oral doses of up to 15.0 mcg/kg (8% of the maximum recommended human daily inhalation dose on a mcg/m^2 basis) were administered to female and male rats. However, triamcinolone acetonide at oral doses of 8 mcg/kg (approximately 4% of the maximum recommended human daily inhalation dose on a mcg/m^2 basis) caused dystocia and prolonged delivery and at oral doses of 5.0 mcg/kg (approximately 2.5% of the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and above caused increases in fetal resorptions and stillbirths and decreases in pup body weight and survival. At a lower dose of 1.0 mcg/kg (approximately 0.5% of the maximum recommended human daily inhalation dose on a mcg/m^2 basis) it did not induce the above mentioned effects.

Pregnancy: Pregnancy Category C. Triamcinolone acetonide has been shown to be teratogenic at inhalational doses of 20, 40, and 80 mcg/kg in rats (approximately 0.1, 0.2, and 0.4 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis, respectively), in rabbits at the same doses (approximately 0.2, 0.4, and 0.8 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis, respectively) and in monkeys, at an inhalational dose of 500 mcg/kg (approximately 5 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Dose related teratogenic effects in rats and rabbits included cleft palate and/or internal hydrocephaly and axial skeletal defects whereas the teratogenic effects observed in the monkey were CNS and/or cranial malformations. There are no adequate and well controlled studies in pregnant women. Triamcinolone acetonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral glucocorticoids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from glucocorticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous steroid dose and many will not need glucocorticoid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when **Azmacort** Inhalation Aerosol is administered to nursing women.

Pediatric Use: Safety and effectiveness have not been established in pediatric patients below the age of 6. Oral corticosteroids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

ADVERSE REACTIONS

The table below describes the incidence of common adverse experiences based upon three placebo-controlled, multicenter US clinical trials of 507 patients (297 female and 210 male adults (age range 18-64)). These trials included asthma patients who had previously received inhaled $beta_2$-agonists alone, as well as those who previously required inhaled corticosteroid therapy for the control of their asthma. The patients were treated with **Azmacort** Inhalation Aerosol (including doses ranging from 200 to 800 mcg twice daily for 6 weeks) or placebo.

Adverse Events Occurring at an Incidence of Greater Than 3% and Greater Than Placebo

Adverse Event	Azmacort Dose			Placebo
	200 mcg bid (n=57)	400 mcg bid (n=170)	800 mcg bid (n=57)	(n=167)
Sinusitis	5 (9%)	7 (4%)	1 (2%)	6 (4%)
Pharyngitis	4 (7%)	42 (25%)	10 (18%)	19 (11%)
Headache	4 (7%)	35 (21%)	7 (12%)	24 (14%)
Flu Syndrome	2 (4%)	8 (5%)	1 (2%)	5 (3%)
Back Pain	2 (4%)	3 (2%)	2 (4%)	3 (2%)

Adverse events that occurred at an incidence of 1-3% in the overall **Azmacort** Inhalation Aerosol treatment group and greater than placebo included:

Body as a whole: facial edema, pain, abdominal pain, photosensitivity

Digestive system: diarrhea, oral monilia, toothache, vomiting

Metabolic and Nutrition: weight gain

Musculoskeletal system: bursitis, myalgia, tenosynovitis

Nervous system: dry mouth

Organs of special sense: rash

Respiratory system: chest congestion, voice alteration

Urogenital system: cystitis, urinary tract infection, vaginal monilia

In older controlled clinical trials of steroid dependent asthmatics, urticaria was reported rarely. Anaphylaxis was not reported in these controlled trials. Typical steroid withdrawal effects including muscle aches, joint aches, and fatigue were noted in clinical trials when patients were transferred from oral steroid therapy to **Azmacort** Inhalation Aerosol. Easy bruisability was also noted in these trials.

Hoarseness, dry throat, irritated throat, dry mouth, facial edema, increased wheezing, and cough have been reported. These adverse effects have generally been mild and transient. Cases of oral candidiasis occurring with clinical use have been reported. (See **WARNINGS.**) Anaphylaxis has also been reported from post-marketing surveillance.

OVERDOSAGE

There are no data available on the effects of acute or chronic overdose. However, acute overdosing with **Azmacort** Inhalation Aerosol is unlikely in view of the total amount of active ingredient present and the route of administration. The maximum total daily dose (1600 mcg) has been well tolerated when administered as a single dose of 16 consecutive inhalations to adult asthmatics in a controlled clinical trial. Chronic overdosage may result in signs/symptoms of hypercorticoidism. (See **PRECAUTIONS.**) The risk of candidiasis could also be increased.

DOSAGE AND ADMINISTRATION

Adults: The usual recommended dosage is two inhalations (200 mcg) given three to four times a day or four inhalations (400 mcg) given twice daily. The maximal daily intake should not exceed 16 inhalations (1600 mcg) in adults. Higher initial doses (12 to 16 inhalations per day) may be considered in patients with more severe asthma.

Children 6 to 12 Years of Age: The usual recommended dosage is one or two inhalations (100 to 200 mcg) given three to four times a day or two to four inhalations (200 to 400 mcg) given twice daily. The maximal daily intake should not exceed 12 inhalations (1200 mcg) in children 6 to 12 years of age. Insufficient clinical data exist with respect to the safety and efficacy of the administration of **Azmacort** Inhalation Aerosol to children below the age of 6. The long-term effects of inhaled steroids, including **Azmacort** Inhalation Aerosol, on growth are still not fully known.

Rinsing the mouth after inhalation is advised.

Different considerations must be given to the following groups of patients in order to obtain the full therapeutic benefit of **Azmacort** Inhalation Aerosol:

Note: **In all patients, it is desirable to titrate to the lowest effective dose once asthma stability has been achieved.**

Patients Not Receiving Systemic Corticosteroids: Patients who require maintenance therapy of their asthma may benefit from treatment with **Azmacort** Inhalation Aerosol at the doses recommended above. In patients who respond to **Azmacort** Inhalation Aerosol, improvement in pulmonary function is usually apparent within one to two weeks after the initiation of therapy.

Patients Maintained on Systemic Corticosteroids: Clinical studies have shown that **Azmacort** Inhalation Aerosol may be effective in the management of asthmatics dependent or maintained on systemic corticosteroids and may permit replacement or significant reduction in the dosage of systemic corticosteroids.

The patient's asthma should be reasonably stable before treatment with **Azmacort** Inhalation Aerosol is started. Initially, **Azmacort** Inhalation Aerosol should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid is started by reducing the daily or alternate daily dose. Reductions may be made after an interval of one or two weeks, depending on the response of the patient. A slow rate of withdrawal is strongly recommended. Generally, these decrements should not exceed 2.5 mg of prednisone or its equivalent. During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, *e.g.*, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with the inhaler but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. Inhaled corticosteroids should be used with caution when used chronically in patients receiving prednisone regimens, either daily or alternate day. (See **WARNINGS.**)

During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

Directions for Use: An illustrated leaflet of patient instructions for proper use accompanies each package of **Azmacort** Inhalation Aerosol.

HOW SUPPLIED

Azmacort Inhalation Aerosol contains 60 mg triamcinolone acetonide in a 20 gram package which delivers at least 240 actuations. It is supplied with a white plastic actuator, a white plastic spacer-mouthpiece and patient's leaflet of instructions: box of one. NDC 0075-0060-37. Each actuation delivers 200 mcg triamcinolone acetonide from the valve and 100 mcg from the spacer-mouthpiece under defined *in vitro* test conditions.

Avoid spraying in eyes.

For best results, the canister should be at room temperature before use.

Shake well before using.

CONTENTS UNDER PRESSURE. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw canister into fire or incinerator. Keep out of reach of children unless otherwise prescribed. STORE AT ROOM TEMPERATURE

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs):

> WARNING: Contains CFC-12, a substance which harms public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Information For The Patient" portion of this package insert under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

Caution: Federal law prohibits dispensing without prescription.

Marketed by

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

COLLEGEVILLE, PA 19426

IN-0367J Rev. 6/97

Questions?
Comments?
Call:
1-800-479-5767

INFORMATION FOR THE PATIENT

Your Guide to the

Azmacort®
(triamcinolone acetonide) Inhalation Aerosol

Special Delivery System

Your doctor has prescribed Azmacort® (triamcinolone acetonide) Inhalation Aerosol to help control your asthma. Your Azmacort Inhalation Aerosol is one of the most efficient and easy-to-use devices available to help you take your prescribed medication. Used properly, it will effectively and reliably relieve your asthma symptoms.

To receive the maximum benefit, **it is very important that you carefully read and follow all the instructions contained in this booklet** for the daily use and care of your Azmacort Inhalation Aerosol.

IMPORTANT NOTE: If you've used other metered-dose inhalers before, you may expect the Azmacort Inhalation Aerosol to deliver a noticeable "blast" of medication into your mouth.

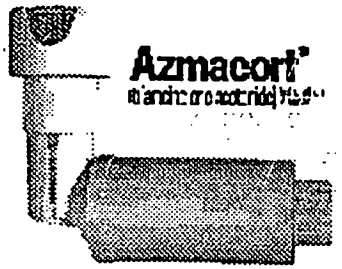
Your AZMACORT Inhalation Aerosol, however, is designed to provide a gentle mist, not a "blast," when used.

This gentle action makes it possible for your medication to be more effectively delivered into the passageways to your lungs, with very little left to linger in your mouth. In fact, you may not even feel the medication entering your mouth, but rest assured, that is how the Azmacort Inhalation Aerosol works.

IMPORTANT: Please read all instructions in this guide carefully before using your Azmacort Inhalation Aerosol.

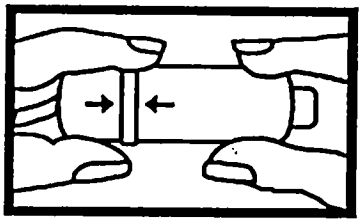
BEFORE STARTING TO TAKE THIS MEDICINE, TELL YOUR DOCTOR:

- If you are pregnant or intending to become pregnant.
- If you are breast-feeding a baby.
- If you are allergic to Azmacort Inhalation Aerosol or any other orally inhaled glucocorticoid.
- If you are taking other medications. In some circumstances, this medication may not be suitable and your doctor may wish to give you a different medicine.



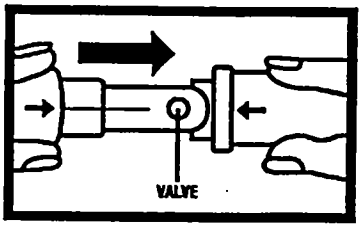
PREPARE YOUR AZMACORT INHALATION AEROSOL INHALER FOR USE

STEP 1



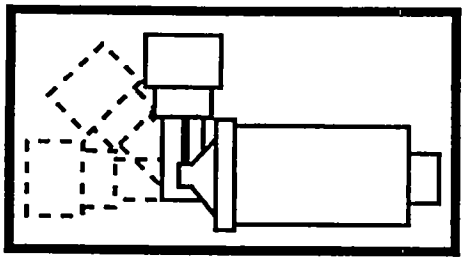
1. Line up the arrows on the inhaler.

STEP 2



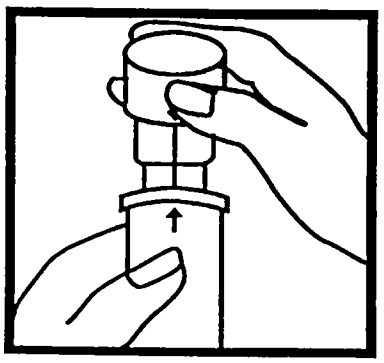
2. Gently pull the inhaler to its fully extended position. You will see the valve (small hole) where the medication will come out.

STEP 3



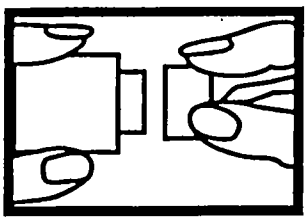
3. Adjust the inhaler into an "L" shape. It is hinged to swing in one direction only.

STEP 4



4. The ridge on the top part of the inhaler should fit into the notch on the bottom part.

STEP 5



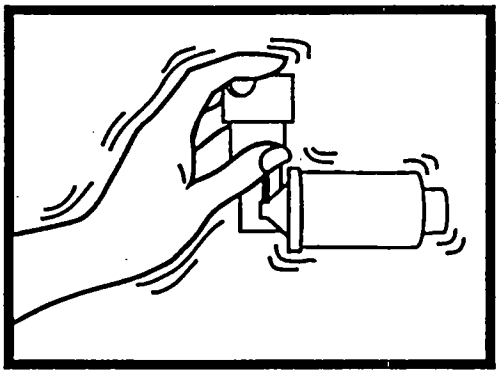
5. Remove the mouthpiece cap.

To prepare your Azmacort Inhalation Aerosol for use, the inhaler must be primed prior to the first use. To prime, hold the inhaler upright, with the mouthpiece facing away from you. Shake the inhaler gently, then press the canister firmly and quickly. Repeat this procedure again so a total of 2 puffs are released. Your Azmacort Inhalation Aerosol is now ready for use.

Repriming is only necessary when your inhaler has not been used for more than 3 days. To reprime, shake the inhaler and release one puff. Repeat this procedure again so a total of two puffs are released.

USING YOUR AZMACORT INHALATION AEROSOL INHALER

STEP 6

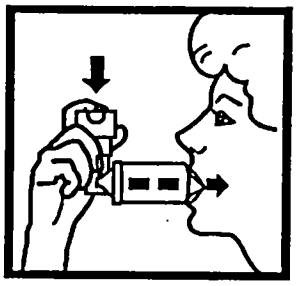


6. The metal Azmacort canister has already been inserted into the inhaler. Once you have opened the inhaler, shake it well before each use. **IMPORTANT: You must shake the inhaler each and every time before inhaling the medication.** If your doctor has instructed you to take more than one breath of medication at a time, **you must shake the inhaler EACH TIME before each inhalation of medication, NOT JUST ONCE.**

STEP 7

7. Breathe out to empty your lungs completely before using the inhaler! This is important to make sure that you can breathe the medication deeply into your lungs.

STEP 8



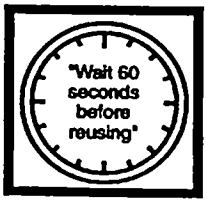
8. Place mouthpiece into your mouth, and close your lips tightly around it. Press down firmly and steadily on the metal canister while breathing in slowly and deeply **THROUGH YOUR MOUTH ONLY.** (If necessary, pinch your nose closed.) Be sure to release your finger pressure from the top of the canister after the medication is released.

Remember, the Azmacort Inhalation Aerosol delivers a **gentle mist** of medication, so don't be surprised if you hardly feel it.

Do not remove the inhaler from your mouth after breathing in the medication. Hold your breath for 10 seconds with the inhaler STILL in your mouth, THEN remove the inhaler and breathe out very slowly.

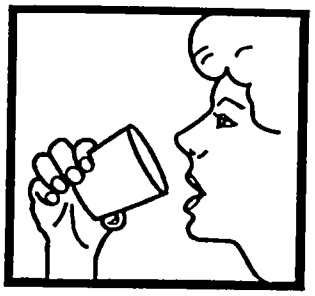
Unlike the other inhalers you may have used, you will not feel the medication impact the back of your mouth. This is because of the unique design of the Azmacort Inhalation Aerosol delivery system.

STEP 9



9. If your doctor has told you to take more than one breath of medication at a time: **WAIT AT LEAST 60 SECONDS** between each one, then start again at Step 6.

STEP 10



10. After the prescribed number of inhalations, thoroughly rinse out your mouth with water. **NOTE:** If your mouth becomes sore or develops a rash, be sure to mention this to your physician, but do not stop using your inhaler unless instructed to do so.

DOSAGE: USE ONLY AS DIRECTED BY YOUR PHYSICIAN

WARNING: Azmacort® (triamcinolone acetonide) Inhalation Aerosol contains medication that is intended for treatment of your asthma. It does *not* contain medication intended to provide rapid relief of your breathing difficulties during an asthma attack.

It is very important that you use Azmacort Inhalation Aerosol regularly at the intervals recommended by your doctor, and not as an emergency measure. Your physician will decide whether other medication is needed, should you require immediate relief.

CAUTION: CONTENTS OF CANISTER UNDER PRESSURE.

Do not puncture. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw canisters into a fire or incinerator. Please keep out of the reach of children.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs):

This product contains CFC-12, a substance which harms the environment by destroying ozone in the upper atmosphere.

Your physician has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN.** If you have any questions about alternatives, consult with your physician.

IMPORTANT TIPS FOR USING YOUR AZMACORT INHALATION AEROSOL INHALER

- Always use only as directed by your physician. Do not use it more often than instructed; do not skip doses.

- Follow all instructions in this booklet very closely and carefully for best results, especially those for use and cleaning.
- Remember, repriming is only necessary when the inhaler has not been used for more than 3 days. To reprime, shake the inhaler gently and release one puff. Repeat this procedure again so that a total of two puffs have been released. Do not reprime between more frequent usage.

- **Please Note:**
  You will receive a new Azmacort Inhalation Aerosol unit each time you refill your prescription.This is done to assure optimal working order of the unique Azmacort Inhalation Aerosol spacer device/delivery system. In addition, a new Azmacort Inhalation Aerosol will guard against a build-up of the drug on the barrel portion of the device, maximizing the cleanliness of your unit. The cost of Azmacort Inhalation Aerosol is MINIMALLY affected by including a new inhaler with each prescription.

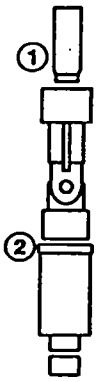
STORING YOUR AZMACORT INHALATION AEROSOL INHALER

- Keep your inhaler **out of the reach of children,** unless otherwise prescribed.
- Store your Azmacort Inhalation Aerosol, including the metal canister, at room temperature.
- Protect from freezing temperatures and direct sunlight.
- For best results, the canister should be at room temperature before use.
- **DO NOT** use after the date shown as "EXP" on the label or box.
- Azmacort Inhalation Aerosol canisters are for use with Azmacort Inhalation Aerosol actuators and spacer-mouthpieces only. The actuator and spacer-mouthpiece should not be used with other aerosol medications.
- **REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.**

DAILY CARE OF YOUR AZMACORT INHALATION AEROSOL INHALER

Your Azmacort Inhalation Aerosol **MUST** be cleaned in lukewarm water only once each day to avoid build-up of medication particles in the inhaler that can block the puff of medication and interfere with proper operation. The use of soap, detergents, or disinfectants is unnecessary.

1. **IMPORTANT:Remove metal canister from inhaler.** Pull canister straight out from inhaler and place aside. **Canister must be removed for proper cleaning of inhaler.**
2. Pull apart remaining two plastic parts of inhaler, remove mouthpiece cap, and gently wash in lukewarm water. **Dry thoroughly.**
3. Snap the two plastic parts of the inhaler back together; push closed. Replace mouthpiece cap. Reinsert metal canister by gently turning while inserting. The canister should fit snugly without falling out.



HOW TO CHECK CONTENTS OF YOUR CANISTER

Shaking the canister will **NOT** give you a good estimate of how much Azmacort® (triamcinolone acetonide) Inhalation Aerosol is left.

We have included a convenient check-off chart to assist you in keeping track of medication puffs used. This will help assure that you receive the 240 "Full Puffs" of medication present.

Azmacort® Inhalation Aerosol 240 Puff Check-Off

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140
141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160
161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180
181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200
201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220
221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240

- Retain with medication or affix to convenient location.
- Starting with puff #1, check off one circle for each puff used.
- **DISCARD MEDICATION AFTER 240 PUFFS.**

FURTHER INFORMATION

- This leaflet does not contain the complete information about your medication. *If you have any further questions, or are not sure about something, you should ask your doctor or pharmacist.*
- You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished this canister.

Questions?
Comments?
Call: 1-800-479-5767

Marketed by
RHÔNE-POULENC RORER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

Rev. 6/97

IN-0367J

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18117/S029

MEDICAL REVIEW(S)

AUG 20 1998

NDA 18-117
Azmacort
Triamcinolone Acetonide
Submission Date. 2/26/98

Rhone-Poulenc Rorer
March 1998
Forwarded March 1998
Reviewed 4/15/98
Signed and delivered 8/20/98

RESPONSE TO CONSULT ON A NDA SUBMISSION

Introduction

This review analyzes the growth of asthmatic children treated with Triamcinolone Acetonide (TAA) up to one year. For patients for which height data was missing at month twelve, but available at day 300, were also included in the final analysis by "annualizing" the difference between this day and that expected at day 365. No data are available on growth before patients were randomized into the study, therefore the comparisons made are between growth velocity of patients on the active drug vs. those in the control group. The focus of the analysis is growth velocity, not the therapeutic effects of these medications on the underlying conditions, although the efficacy of these products is clearly relevant to any benefit/risk assessment.

Although sex differences exist in growth patterns during childhood and adolescence, these differences tend not to be as marked during the prepubertal years (4-11 years). Growth velocities for girls at this time are slightly faster than boys, but overall they rarely exceed 5 mm at any growth velocity percentile. In the graphic displays data was segregated by sex, but then combined when displayed in tabular form for ease of viewing.

Although statistical differences between groups are presented, individual growth velocities are shown to illustrate how some patients seem to be more affected by TAA than others. Thus, in trying to understand this adverse reaction, the focus of the illustrations and the review is on individual patients. Although it is possible to see how a patient is growing during the study, the lack of information before randomization does not allow for the estimation of the degree of CS effect on growth in any given individual. Patients growing below a given percentile on the studies could be growing at his/her normal growth velocity (not affected) or affected to a larger or a smaller degree by TAA. Thus, it is possible to make comparisons between groups but not between individuals or between growth velocities before and after drug exposure in the same patient.

In addition, patients growing in excess of 12 cm/year (>7SD for this age group) as well as patients who showed negative growth velocities were excluded from the statistical analyses. Thus, the analysis is not based on the intent-to-treat population.

Study Design and Results

This was a randomized open label, placebo controlled, parallel group in patients with asthma and stratified by severity (ages between 6-11 years old). Data on patients with moderate asthma either treated with non-steroidal medications (n=94) or orally inhaled TAA (n=101) for one year were reviewed.

Children on TAA annual growth velocity was 5.3 $\pm$ 1.6 cm and 6.1 $\pm$ 1.4 cm/year for those treated with non-steroidal medication (delta=0.8 cm/year, p=0.0003). A difference of 0.8 cm/year corresponds to approximately 1 SD.

Each patient growth rate is plotted in a growth velocity chart-either for boys or girls-as well in barcharts to visually display the distribution of all patients in their respective growth velocity percentiles. Finally, a summary table condenses all the results.

The bar-graph of growth velocities suggest that girls seem to be more affected than boys.

Three times more patients in the TAA group grew below the 3rd and 10th and the 25th percentile than in the control group (16% vs. 5%, 32 vs. 9%, and 42% vs. 12% respectively) strongly indicating that TAA is systemically absorbed, that TAA blunts growth rates in a significant manner when compared to conventional therapy.

Patients during the study were allowed to adjust their TAA dose. Thus different patients received distinct doses of the product. As a result, the sponsor has forwarded a dose response analysis that strongly suggest that growth velocities are inversely correlated with dosing.

Summary

The current study indicates that TAA administration at the currently approved dose significantly affect growth rates of children. This effect seems to be dose dependent.

Recommendation

The label should properly reflect the findings that this review discusses.

Enclosures
Bar-graphs for all patients analyzed
Growth velocities for girls and boys
Summary table
Dose response and statistical analysis (copied form the sponsor submission)

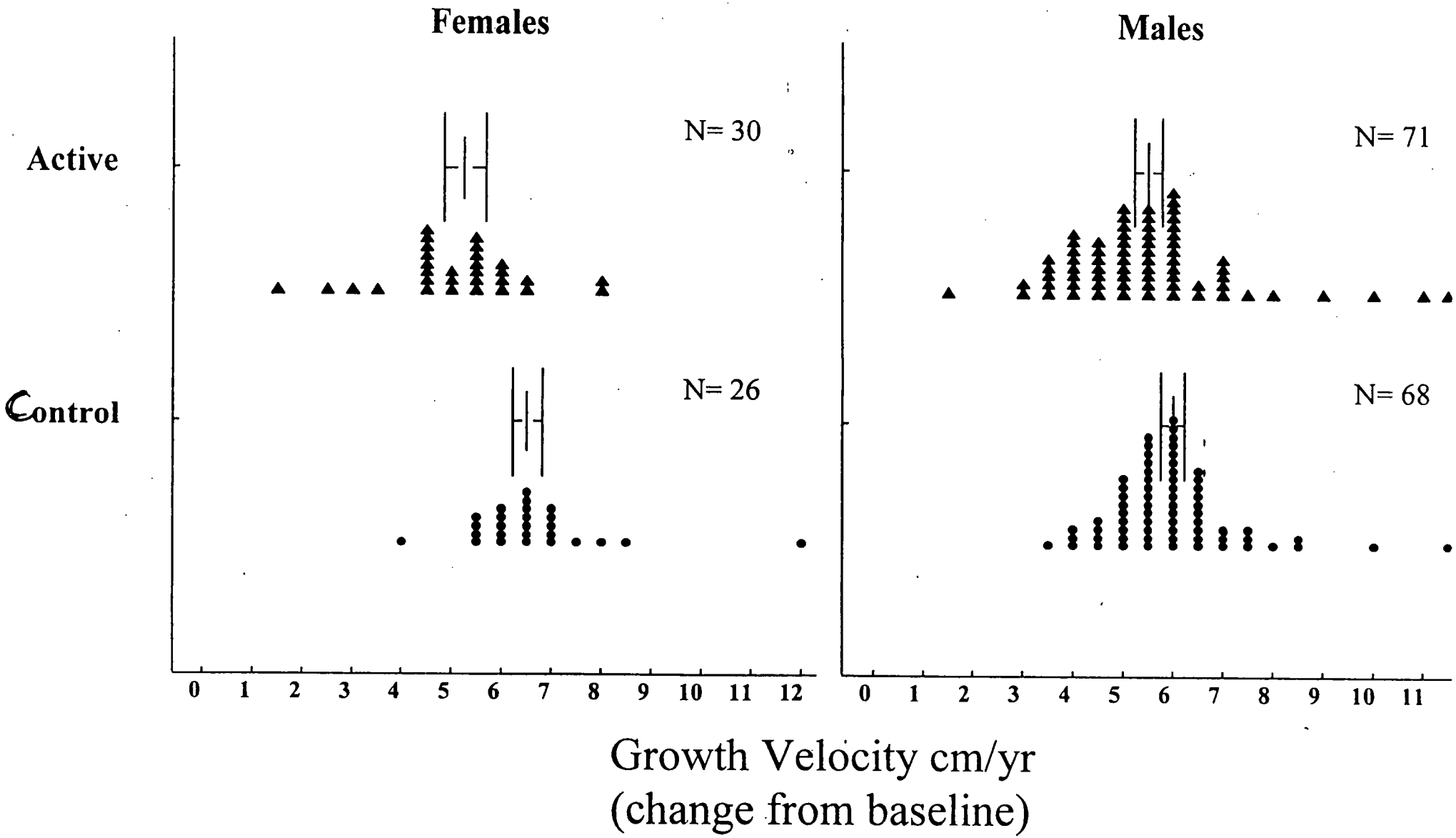
/S/
Saul Malozowski, MD, PhD, MBA
Medical officer
DMEDP-HFD-510
8/20/1998

PS.
Although this document is signed today, the results of this review were shared with the Division of Pulmonary Drug Products one week after its submission to HFD-510. In addition, these analyses were presented during the 8/31/1998, in the combined advisory committee of these divisions.

CC: NDA 18-117
DivFile
HFD570 Meyer
HFD570 Barnes

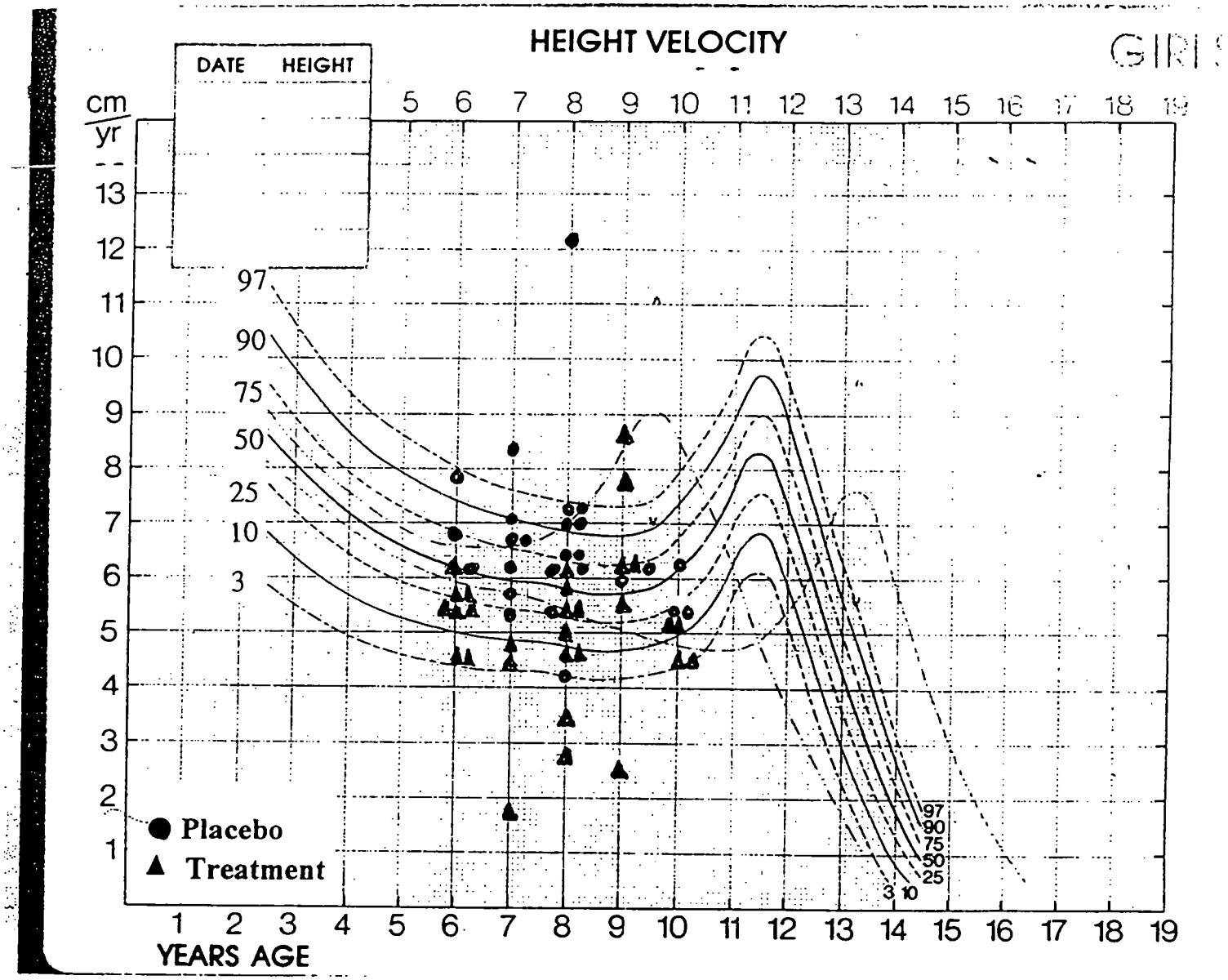
Triamcinolone

Median Growth Velocity
(95% Confidence Intervals)

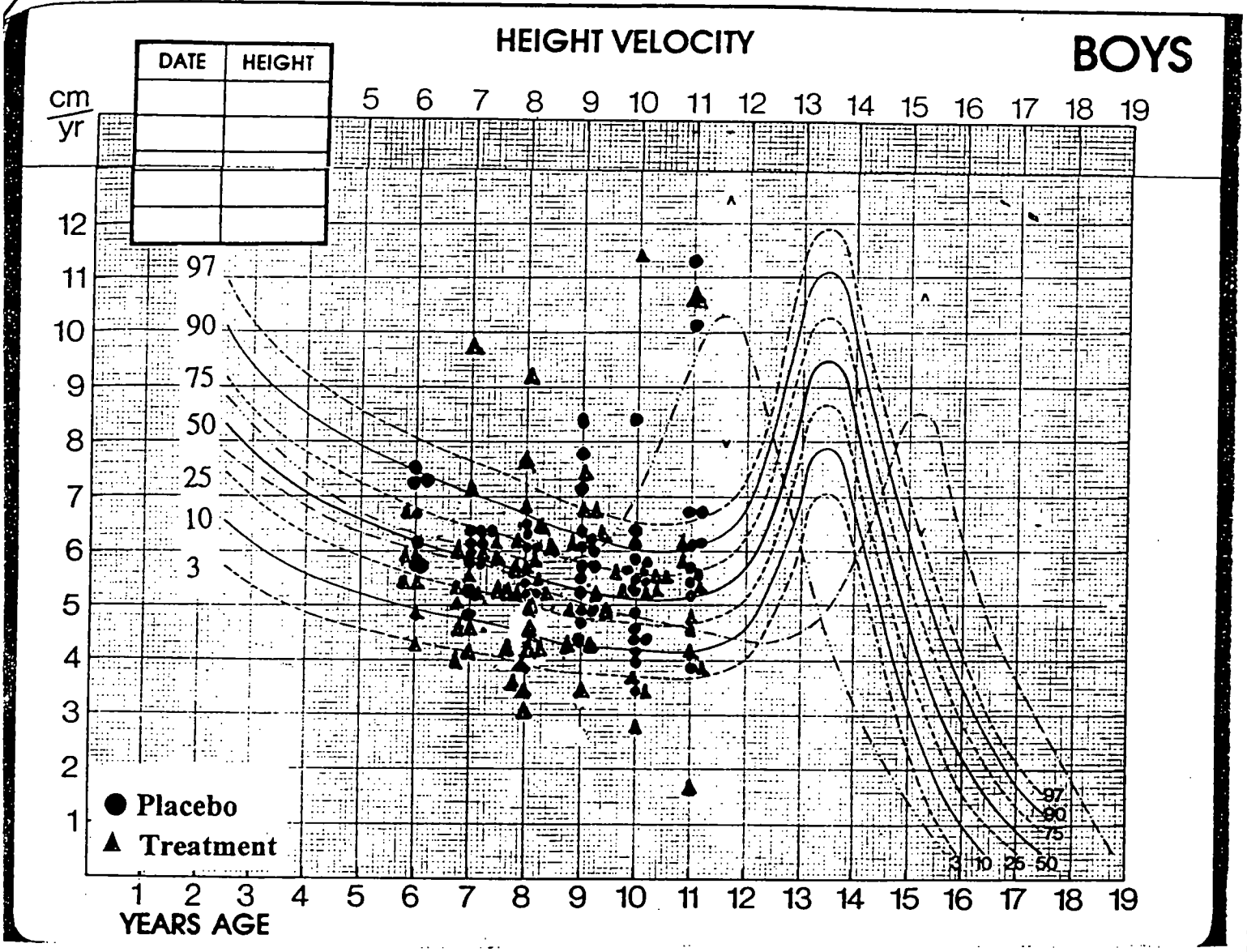


Growth Velocity cm/yr
(change from baseline)

Triamcinolone



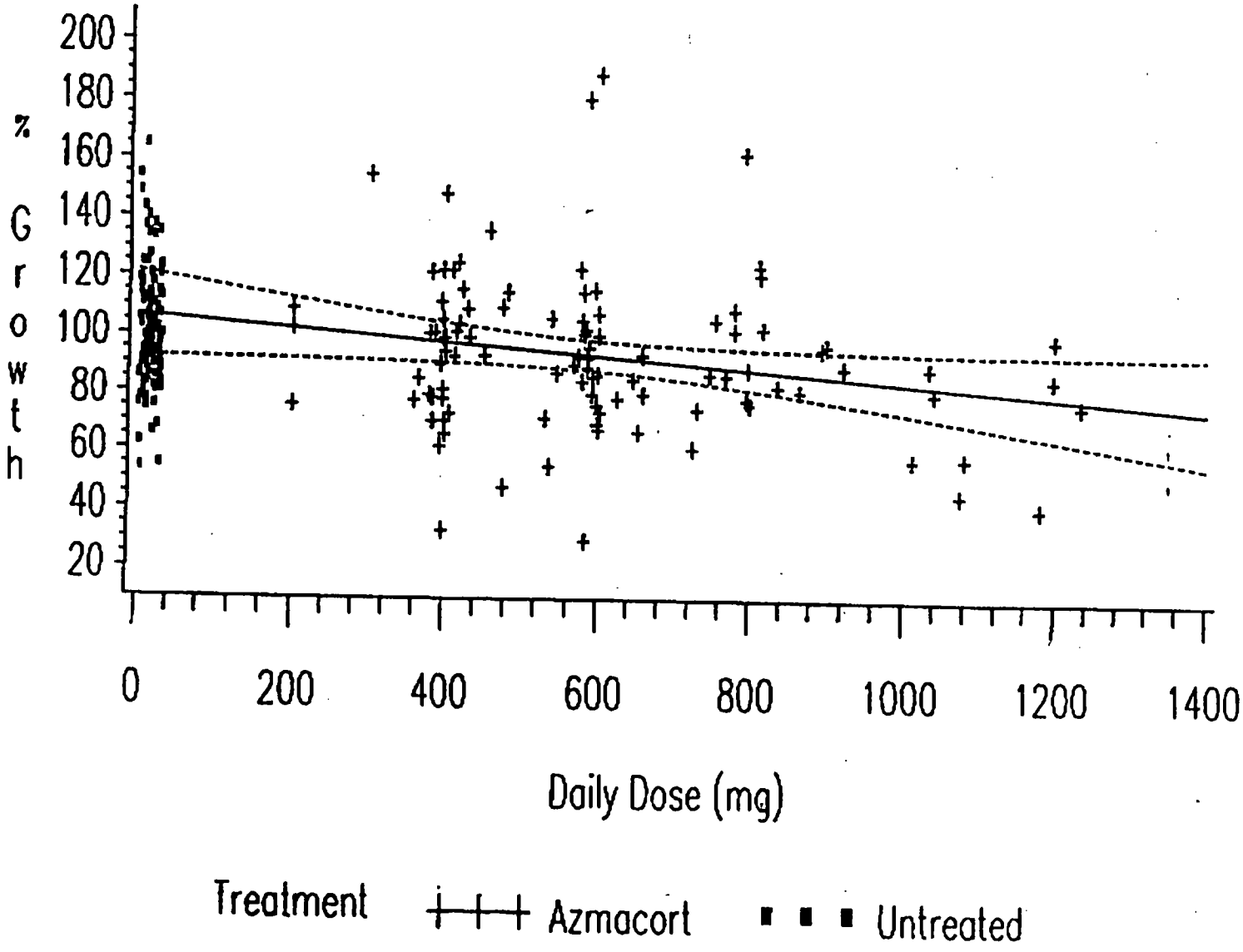
Triamcinolone



Azmacort Summary

Percentile	Control	Triamcinolone
≤ 3	5%	16 %
≤ 10	9 %	32 %
≤ 25	12 %	42 %
≤ 50	35 %	60 %

RG5016-117
Regression of PG on Daily Dose
Azmacort: All Treated >= 10 Mo.



RG5016-117

Regression of % Growth on Average Daily Dose
Azmacort All-Treated >= 10 Mo.

Model: MODEL1
Dependent Variable: PG

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Prob>F
Model	1	2677.18441	2677.18441	3.836	0.0530
Error	99	69101.00308	697.98993		
C Total	100	71778.18748			

Root MSE	26.41950	R-square	0.0373
Dep Mean	93.20027	Adj R-sq	0.0276
C.V.	28.34702		

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
INTERCEP	1	106.677401*	7.36653175	14.481	0.0001
AVGDOSE	1	-0.022496	0.01148642	-1.958	0.0530**

*: Similar to the Non-steroidal mean of 106.08.
Untreated mean: 101.43, Azmacort mean: 93.20

**: One-sided p value is .027, significant.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18117/S029

ADMINISTRATIVE DOCUMENTS

DIV

PROJECT MANAGER LABELING REVIEW

JAN 2 2 1999

NDA 18-117/S-029

Drug Name: Azmacort Inhalation Aerosol

Sponsor: Rhone-Poulenc Rorer

Submission dated: September 3, 1998.

This supplemental application provides for the addition of priming information to the package insert, Information for the Patient, and carton labeling.

The priming data were submitted on March 19, 1997 as correspondence in response to a Phase 4 commitment to S-026. The chemistry review dated July 16, 1997 requested that the applicant submit labeling to reflect the priming information.

I compared the submitted labeling to the last approved labeling, there are no changes to the labeling other then the priming information. The Information for the Patients sheet and carton were revised to accommodate the priming information. This application should be approved.

/S/

Sandy Barnes
Project Manager

.cc: Orig 18-117/S-029
Division File
HFD-570/S. Barnes
HFD-570/
R/D initialed by

1/22/99

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 18117/S029

CORRESPONDENCE

Dio file

NOV - 6 [illegible]

NDA 18-117

Rhone-Poulence Rorer Pharmaceuticals, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19426-0107

Attention: Judith R. Plon
Director
Regulatory Affairs

Dear Ms. Plon:

Please refer to your new drug application (NDA) for Azmacort Inhalation Aerosol.

We also refer to the July 30, and 31, 1998, advisory committee meeting convened with the advisory committees for the Division of Pulmonary Drug Products and the Division of Metabolic and Endocrine Drug Products. At this meeting, the joint advisory committees agreed that language regarding growth suppressive effects should be incorporated into the package insert of all intranasal and orally inhaled corticosteroids. We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of these drugs.

PRECAUTIONS:

General: Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see **PRECAUTIONS, Pediatric Use** section).

Pediatric Use: Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving orally inhaled corticosteroids, including *(insert product name)*, should be monitored routinely (e.g. via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective

noncorticosteroid treatment alternatives. To minimize the systemic effects of orally inhaled corticosteroids, including *(insert product name)*, each patient should be titrated to his/her lowest effective dose.

ADVERSE REACTIONS:
Cases of growth suppression have been reported for orally inhaled corticosteroids *[(including (insert product name, if appropriate)]* (see **PRECAUTIONS, Pediatric Use** section).

In addition, if you have data from randomized, adequately controlled clinical trials specific to the growth effects of Azmacort, we request that you incorporate this information into the PRECAUTIONS, Pediatric Use subsection as appropriate.

Submit draft labeling in the form of a prior approval supplement to this application. Please incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

This supplement should be submitted within 60 days.

If you have any questions, contact Mr. David Hilfiker, Project Manager, at (301) 827-1046.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research